ASCPT Annual Meeting
Open Forum
March 6, 2013

Contemporary Issues in Clinical Pharmacology

The FDA Office of Clinical Pharmacology Experience

Office of Clinical Pharmacology (OCP)
OTS, CDER, FDA

Agenda

- **Introduction:** Shiew-Mei Huang, PhD
- **Model-Informed Drug Development and Regulatory Review:** Vikram Sinha, PhD
  Panel: Nitin Mehrotra, PhD, Ping Zhao, PhD
- **Development and Regulatory Evaluation of Targeted Therapies:** Michael Pacanowski, PharmD, MPH
  Panel: Issam Zineh, PharmD, MPH
- **Pediatric Drug Development:** Dionna Green, MD
  Panel: Kevin Krudys, PhD
- **Closing Remarks:** Issam Zineh, PharmD, MPH

Contemporary Issues in Clinical Pharmacology:

Introduction

Shiew-Mei Huang, PhD
Deputy Director
Office of Clinical Pharmacology
OTS, CDER, FDA

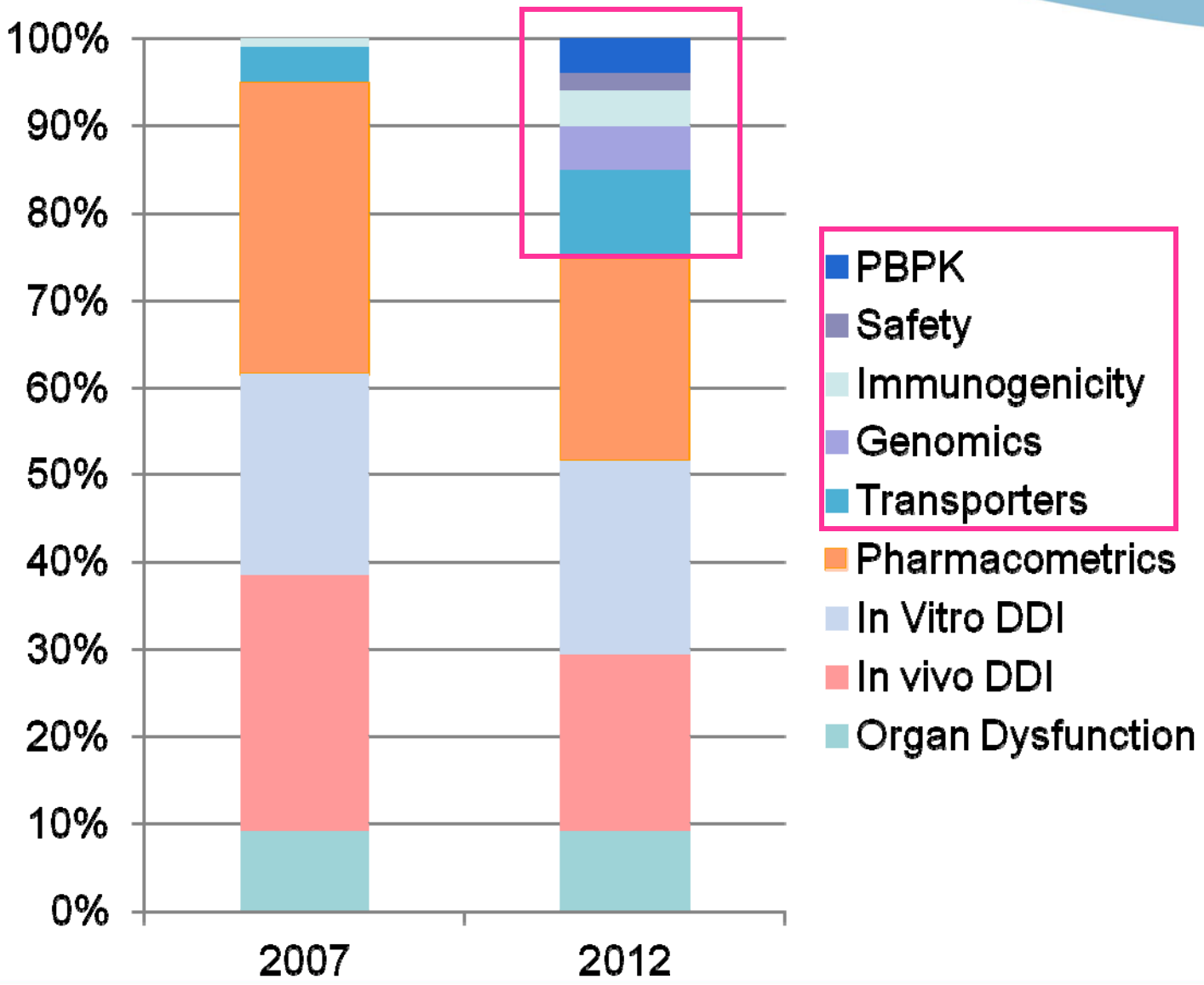
OCP Organization

→Enhance drug development & promote regulatory innovation through applied clinical pharmacology

What Do We Do?

- Our reviewers serve as integrated members of CDER review teams and provide
  - Decision support in the review of therapeutics
  - Mechanistic based guidance in drug development
- In 2012, OCP reviewed > 2,700 IND and 900 NDA/BLA submissions
  - Increased complexity in IND and NDA/BLA reviews
  - Steady increase in pharmacometric, organ dysfunction, drug interaction evaluations [standard] and physiologically-based pharmacokinetic (PBPK), pharmacogenomics, immunogenicity, transporter and mechanistic safety reviews [new areas]

NDA/BLA Reviews



OCP Organization

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Contemporary Issues in Clinical Pharmacology:

Model-Informed Drug Development and Regulatory Review

Vikram Sinha, Ph.D,
Director
Division of Pharmacometrics
Office of Clinical Pharmacology
OTS, CDER, FDA

Outline

- Pharmacometrics at the FDA
- Evolution of pharmacometrics and current scope
- Future Directions
- Research Initiatives and Opportunities In the Division of Pharmacometrics

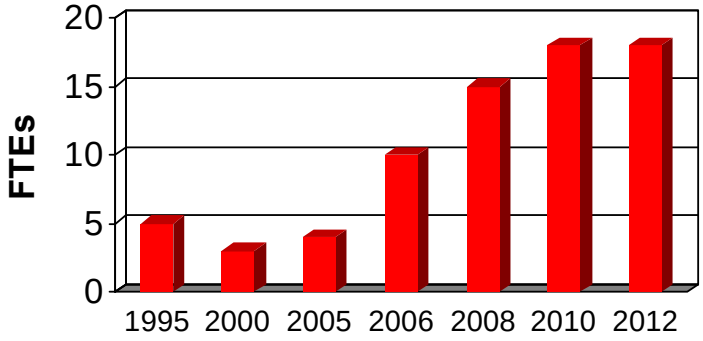
Pharmacometrics: A Quantitative Discipline at FDA

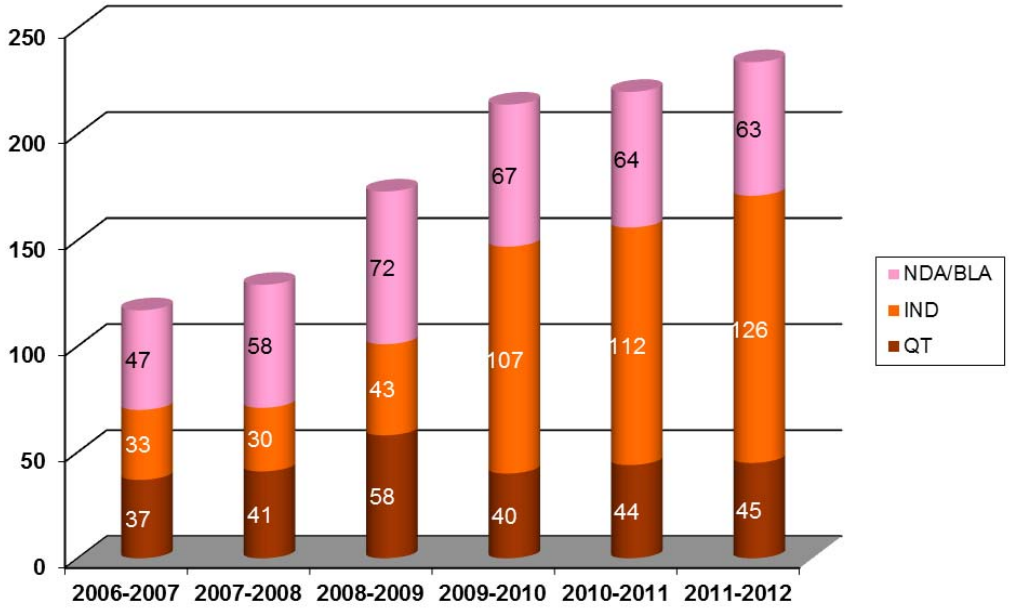
- **Quantitative pharmaco-statistical analysis to answer clinical drug development, regulatory questions and influence decisions**
- **Influence decisions across INDs and Review continuum**
- **Scientists who do this work usually have background in clinical pharmacology/PKPD, biostatistics and have good judgment in the science of regulatory and drug development**

FDA Pharmacometrics Evolution

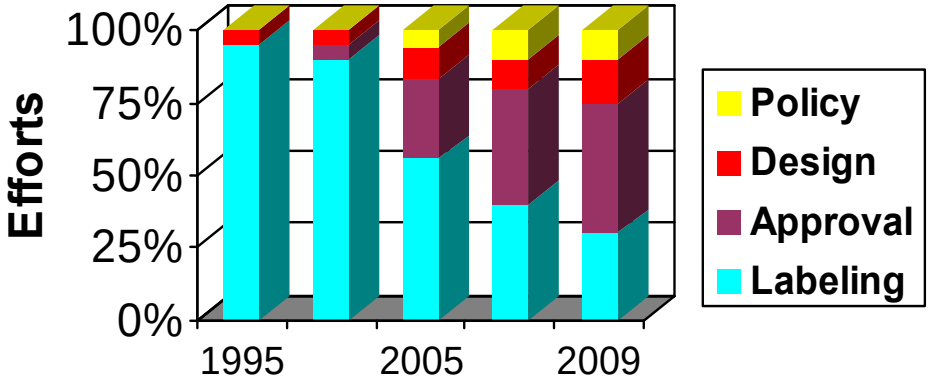
Team→Staff→Division

Resources

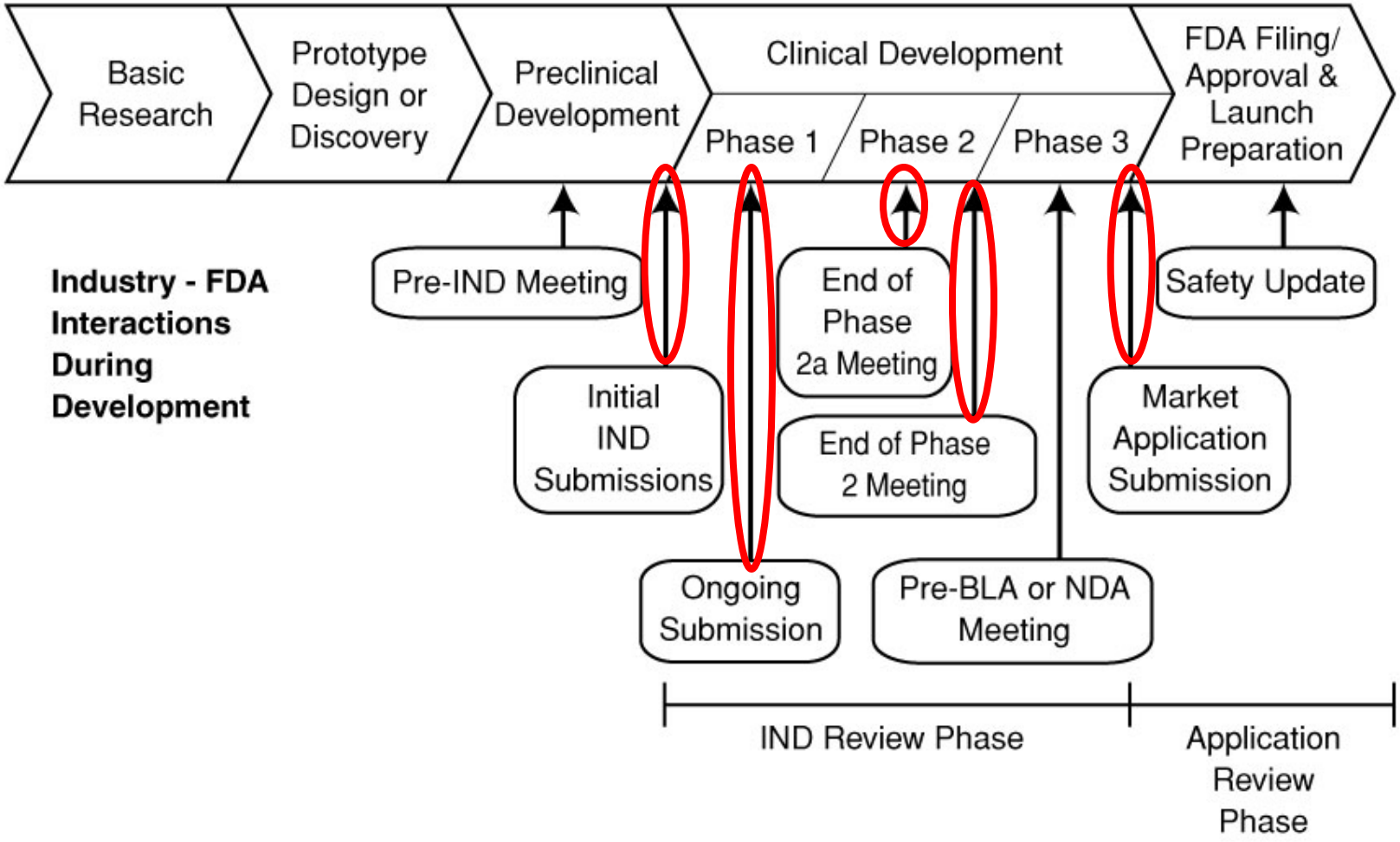




Focus



Multiple Points of Interactions with Sponsors



Pharmacometrics: Current Scope

Tasks	Decisions Influenced

• NDA Reviews
• Protocols
  – Dose-Finding trials
  – Registration trials
• QT Reviews
• Central QT team
• EOP2A Meetings
• Disease Models
  – Knowledge Management
	• Evidence of Effectiveness
	• Labeling
	• Quantify benefit/risk
	  – Target Patients
	  – Dose optimization
	  – Dose adjustments
	• Trial design

The Division has extensively published: Reviews, Commentaries and Scientific articles on its impact and influence in a collaborative manner

Pharmacometric - Key Decisions

Review	Impact
Oxcarbazepine Extented-Release	• Exposure-Response (ER) as evidence to approve lower dose that did not meet statistical significance • Dosing nomogram for pediatrics
Adalimumab	• ER as evidence to explore higher induction doses • PMR issued to explore efficacy and safety of higher induction dosing regimens
Lixivaptan	• Extensive exposure/baseline Na-response analyses across two NDAs to compare efficacy between two drugs led to Complete Response
Truvada	• Adherence-response to support efficacy • Presentation at AC meeting and impact of adherence included in the label
Ambien Controlled-Release	• E-R analyses on multiple pshycometric measurements led to label change in dose adjustment in female patients (will be published soon) (Note: these examples are a sample)

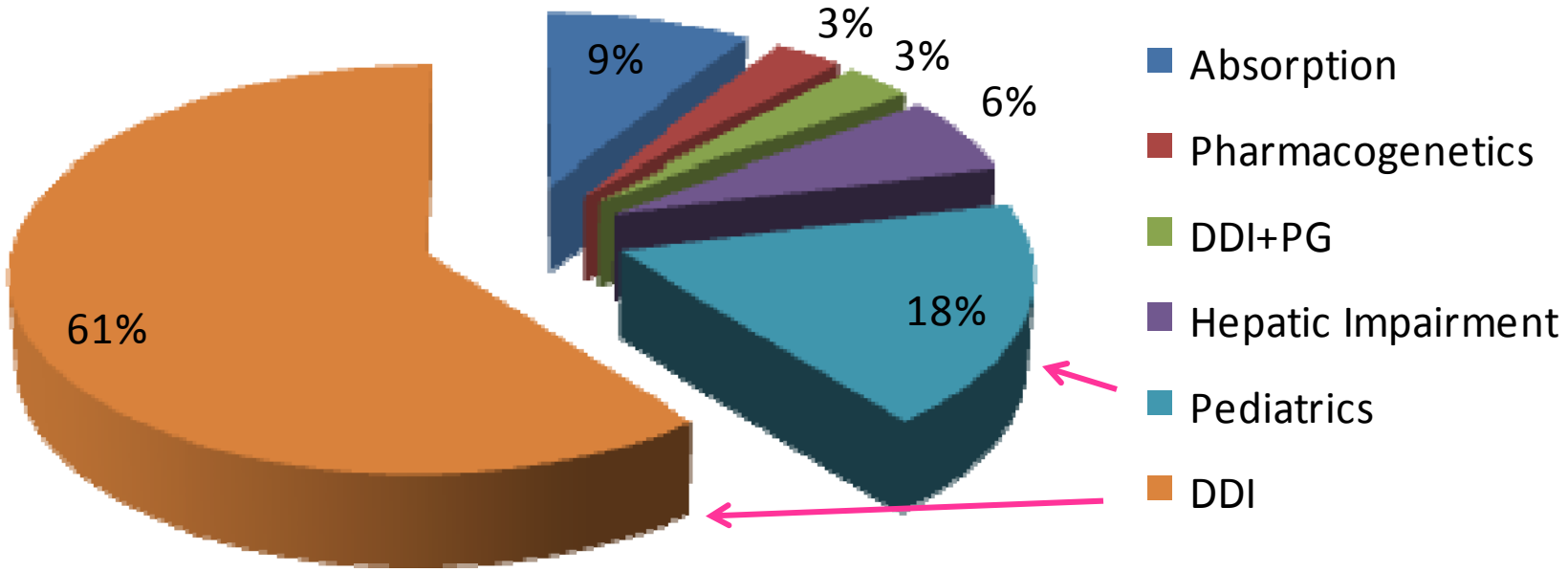
Pharmacometric-Guided Pediatric Dosing Regimens

Approaches for Dosing Regimen	Examples of Specific Drugs
Matching Drug Exposure in Children to Adult Exposure at Labeled-Dose	Busulfex® (ibusulfan) Injection, Zosyn® (piperacillin/tazobactam), Lovaquin® (levofloxacin), Videx® (didanosine), Xyzal® (levocetirizine), Digoxin Elixar, Protonix® (pantoprazole sodium), Nexium IV® (esomeprazole)
Exposure-response of biomarker or clinical endpoint data	Betapace® (sotalol) and Argatroban Injection® (argatroban), Trileptal® (oxcarbazepine)
Effectiveness study plus matching drug exposures	Celebrex® (celecoxib), Humira® (adalimumab), Ilaris® (canakinumab), and Corlopam® (fenoldopam)

Source: H.H.C. Kimo, C. Peck, Clinical Trial Simulations. AAPS Press, (2010).

FDA Reviews are at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

Regulatory Submissions with PBPK Data



Area of applications in the 33 PBPK submissions in IND/NDA received by FDA's Office of Clinical Pharmacology from 2008-12

Huang, Abernethy, Wang, Zhao, Zineh, J Pharm Sci (submitted)

Future Directions

- The division will continue to grow both in size and scope under the current Office of Clinical Pharmacology (OCP), Office of Translational Sciences and CDER leadership.

- Key guidance within the purview of the division will be revisited and if necessary revised
- In addition to efforts to systematically implement the role of drug-disease models in the drug development process, new scientific tools such as systems pharmacology (PBPK, physiologically based pharmacodynamic models) will be assessed
- The division will look to increase its involvement in the IND phase. Specifically, develop scientific tools/approaches, collaborate with sponsors earlier in the development process thereby looking to help get important products earlier to patients

Research Initiatives and Opportunities in Pharmacometrics

- A strong collaborative environment for Reviewers, Programmer contractors and Fellows work and other divisions at the FDA
- Staff have excellent opportunities to develop their technical and scientific knowledge base and enhance their communication and decision-making skills
- Ongoing research initiatives and collaborations in the area of Huntingtons, bipolar disorder, HCV/HIV, cardiac safety and pediatrics, breast cancer, non-inferiority for anti-infectives, hepatic safety, exposure-response for biosimilars. This year, CAMD initiative will look to complete its first platform (tools, methods) in Alzheimers' disease
- Opportunities to publish and participate in external meetings and conferences.

Acknowledgements

Contributions from the Division of Pharmacometrics, Office of Clinical Pharmacology and Review Divisions

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Division of Pharmacometrics
Office of Clinical Pharmacology
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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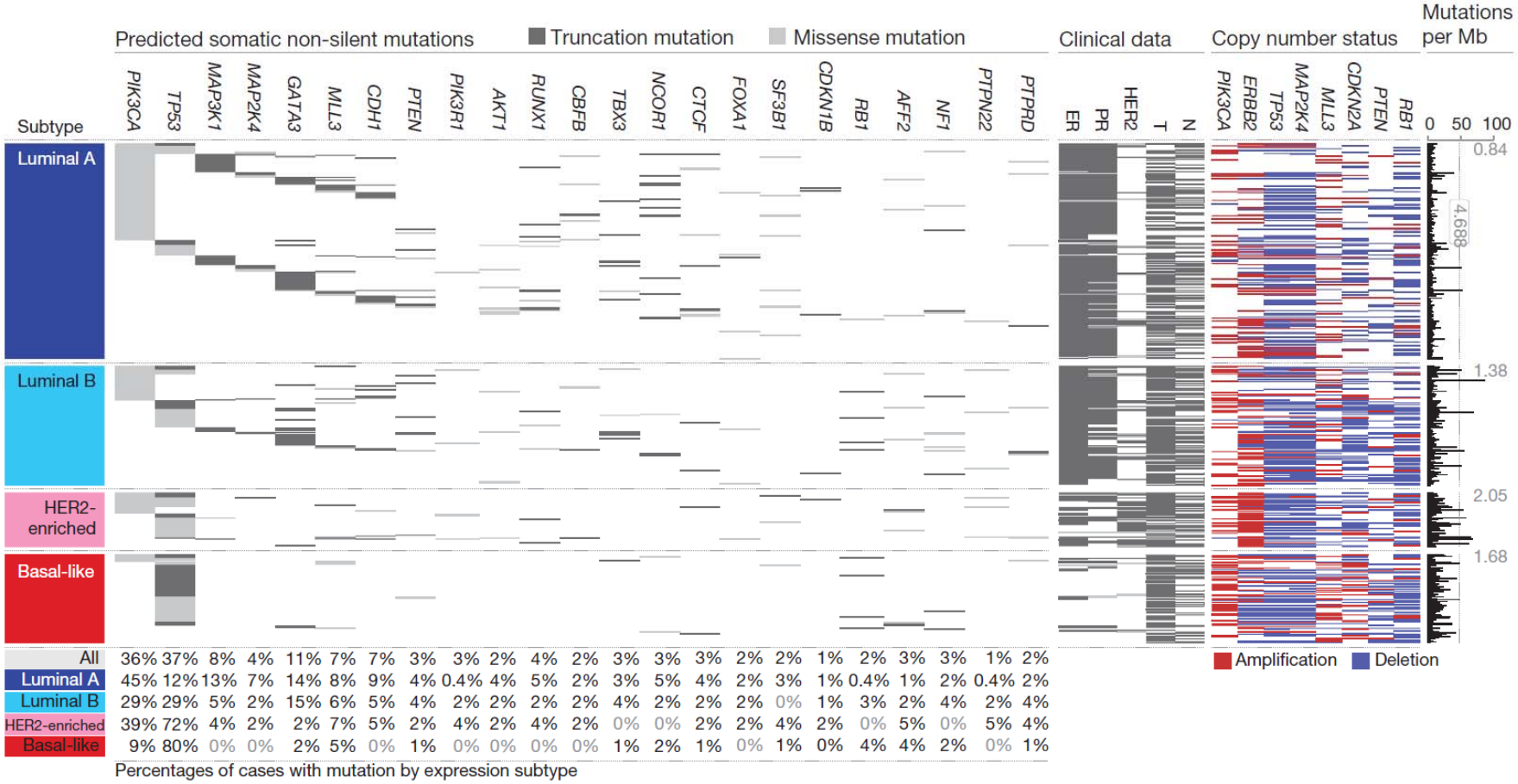
Contemporary Issues in Clinical Pharmacology:

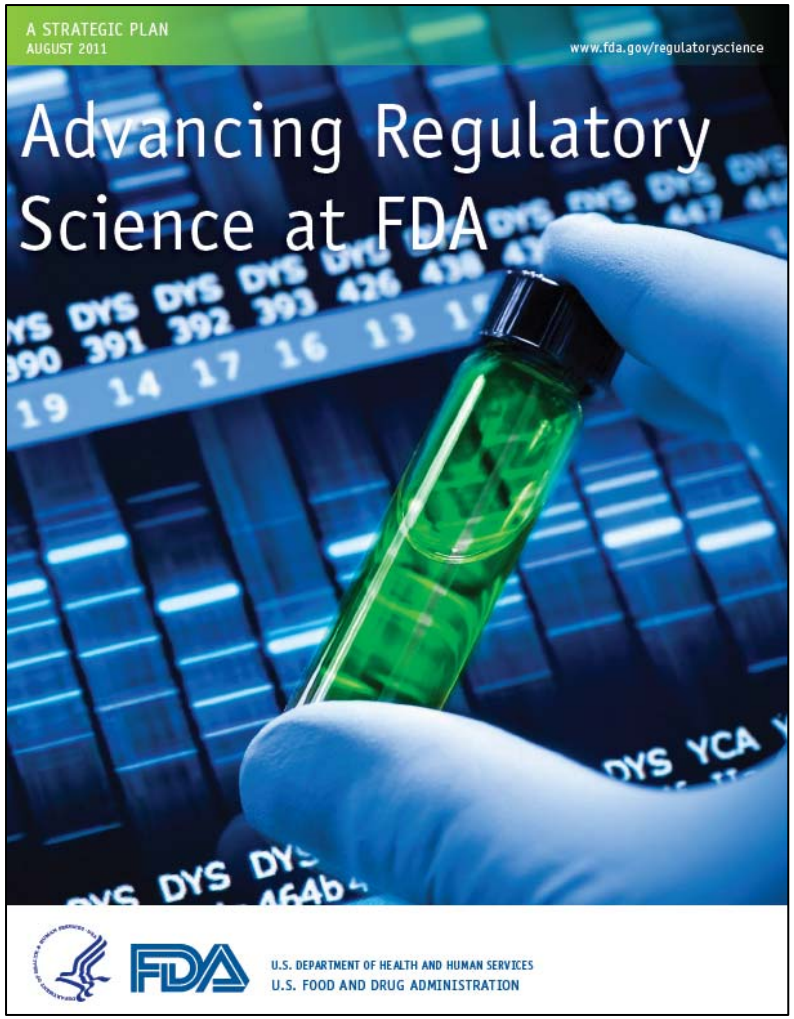
Development and Regulatory Evaluation of Targeted Therapies

Mike Pacanowski, PharmD, MPH
Office of Clinical Pharmacology
Office of Translational Sciences
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Our Future

Targeting the Molecular Basis of Disease





Regulatory Science

Developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance

Vision

Speed innovation, improve regulatory decision-making, and get products to people in need

Focus

Innovation in clinical evaluations and personalized medicine to improve product development and patient outcomes (e.g., trial design, biomarker qualification)

PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013 THROUGH 2017

IX. ENHANCING REGULATORY SCIENCE AND EXPEDITING DRUG DEVELOPMENT

A. Promoting Innovation Through Enhanced Communication Between FDA and Sponsors During Drug Development

B. Advancing the Science of Meta-Analysis Methodologi

C. Advancing the Use of Biomarkers and Pharmacog

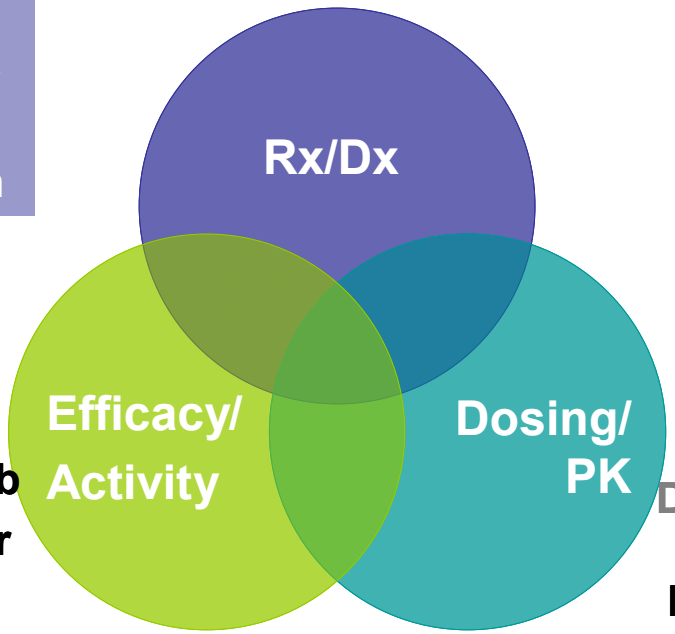
D. Advancing Development of Patient-Reported Outcom Assessment Tools

E. Advancing Development of Drugs for Rare Diseases

Develop capacity
Train staff
Public meeting

NME Genomic Data Submissions FY/CY2012

1/3 of approved NMEs contained genomic biomarker information in the original submission



Rx/Dx
Ivacaftor
Omacetaxine
Ponatanib

Efficacy/ Activity
Vismodegib
Florbetapir
Bosutinib
Regorafenib
Cabozantinib

Dosing/ PK
Clobazam
Deferiprone
Axitinib
Lorcaserin
Mirabegron
Teriflunomide
Tofacitinib

1QFY12
4QCY12

* Biomarker-related labeling

Targeted Therapy Successes… Ushering the Next-Generation of Drugs

- Many approved drugs target biomarker-defined subgroups of patients
- Contemporary examples have introduced major treatment advances

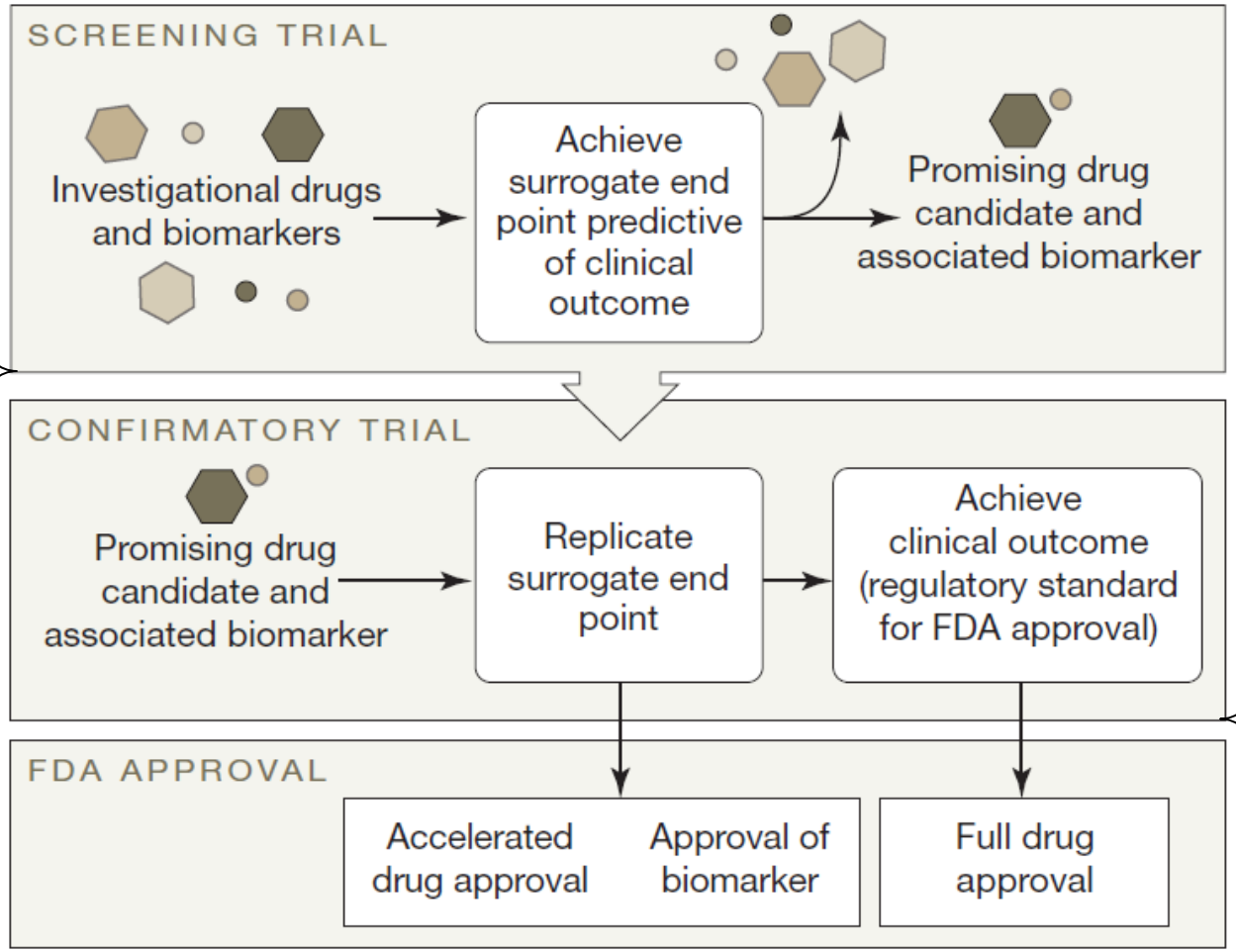
Seamless "Learn/Confirm" Pathway to Targeted Therapies

Enrichment

Prognostic

Predictive

Practical



Companion Diagnostic

Esserman, Woodcock. JAMA 2011 [PMID: 22187281]; Temple. CPT 2010 [PMID: 20944560]

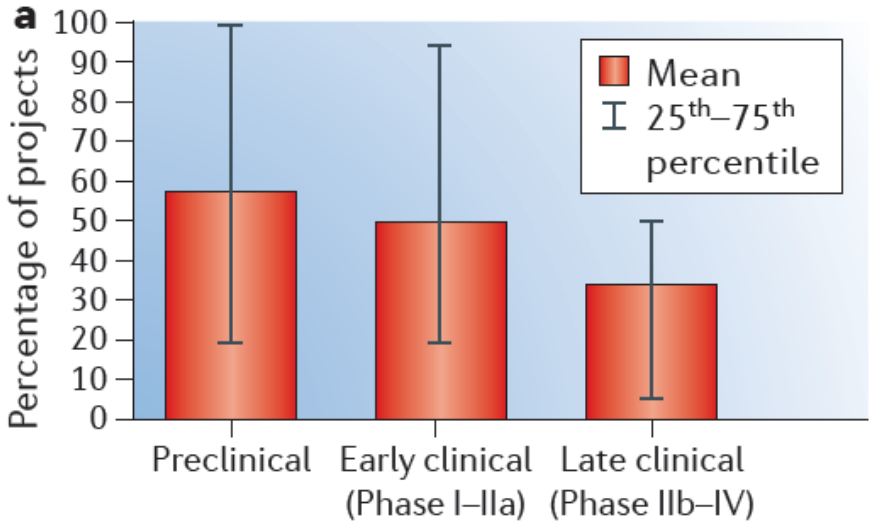
Setting the Stage for Targeted Drug Development

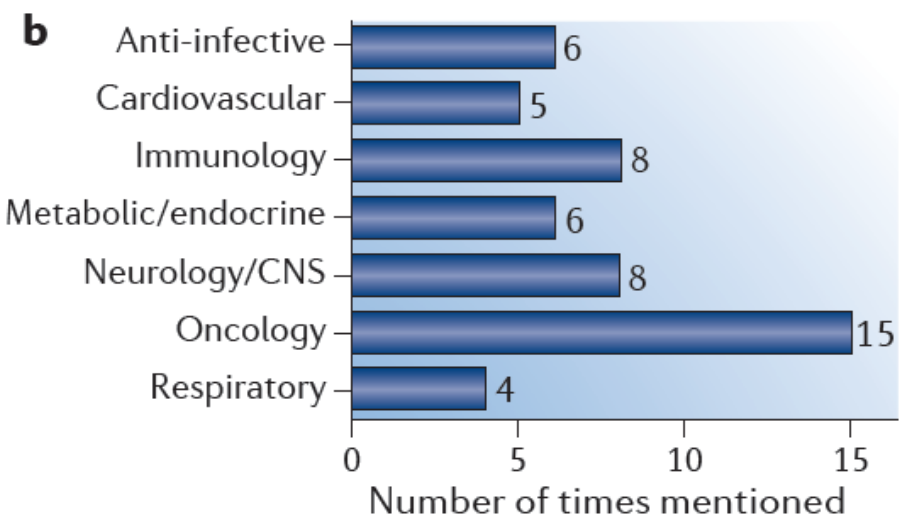
Biomarker is the major pathophysiological driver of the disease
Limited or adverse paradoxical activity of the drug is seen in a subgroup identified through in vitro or animal models (e.g., cell lines or animals)
Biomarker is the known molecular target of therapy
Preliminary evidence of harm from early phase clinical studies in patients without the biomarker
Preliminary evidence of lack of activity from early phase clinical studies in patients without the biomarker
Preliminary evidence of modest benefit in an unselected population, but the drug exhibits significant toxicity

Targeted Therapy Is Not a New Concept

Drug	Therapeutic Area	Biomarker	Label timing
Brentuximab Vedotin	Oncology	CD30	Pre-approval
Cetuximab, Panitumumab	Oncology	EGFR; KRAS	Pre-/Post-approval
Crizotinib	Oncology	ALK	Pre-approval
Exemestane, Fulvestrant, Letrozole	Oncology	ER/PR	Pre-approval
Imatinib	Oncology	C-Kit, PDGFR, FIP1L1	Pre-approval
Ivacaftor	Pulmonary	CFTR	Pre-approval
Lapatinib, Pertuzumab, Trastuzumab, Everolimus	Oncology	HER2	Pre-approval
Tositumomab	Oncology	CD20 antigen	Pre-approval
Vemurafenib	Oncology	BRAF	Pre-approval
Lenalidomide	Hematology	Chromosome 5q	Pre-approval
Maraviroc	Antivirals	CCR5	Pre-approval
Nilotinib, Dasatanib, Imatanib	Oncology	Ph Chromosome	Pre-approval
Arsenic Trioxide, Tretinoin	Oncology	PML/RARα	Pre-approval
Denileukin Diftitox	Oncology	CD25/IL2	Pre-approval
Capecitabine, Fluorouracil	Oncology	DPD	Post-approval
Pimozide, Aripiprazole, Iloperidone, Tetrabenazine, Thioridazine	Psychiatry, Neurology	CYP2D6	Post-approval
Celecoxib	Analgesics	CYP2C9	Pre-approval
Citalopram	Psychiatry	CYP2C19	Post-approval
Rasburicase	Oncology	G6PD	Pre-approval
Valproic Acid	Psychiatry	UCD	Post-approval

Personalized Medicine Strategies: Industry Survey





Comprise 12-50% of company pipelines

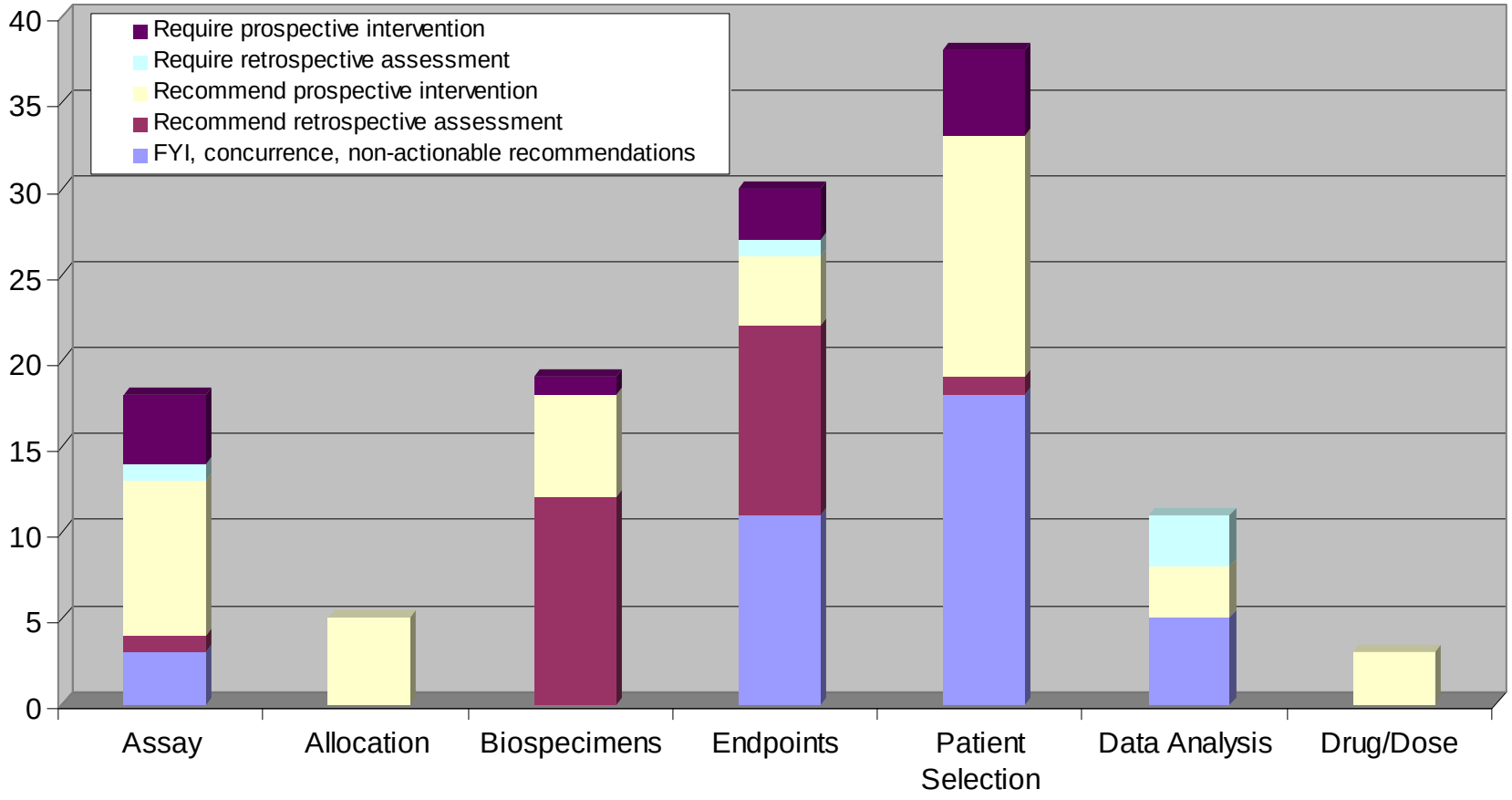
Mostly for internal decision-making

<10% of projects are "stratified"

Policy and Guidance

2005	Guidance on PG Data Submissions
	Concept Paper on Drug-Diagnostic Co-Development
2007	Companion Guidance on PG Data Submissions*
	Guidance on PG Tests and Genetic Tests for Heritable Markers
2010	ICH E16 Concept Paper on PG Biomarker Qualification: Format and Data Standards
	Guidance on Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment
	Guidance on Qualification Process for Drug Development Tools
2011	Guidance on in vitro Companion Diagnostic Devices*
	Guidance on Clinical Trial Designs Employing Enrichment Designs*
2013	Guidance on Clinical PG: Premarketing Evaluation in Early Phase Clinical Studies
In Process	Guidance on Drug-Diagnostic Co-development

Advice to Sponsors CY2012



OCP-Genomics

Strategic Priorities 2013

- **Drug evaluation**
  - Genetic liabilities, biomarker utility, early-phase trial design, co-development
- **Policy and guidance**
  - Policy gaps, implementation of new/emerging policies
- **In/outreach**
  - Intercenter coordination, staff training, international harmonization, human capital
- **Regulatory science**
  - Intra-/extramural research, new resources, knowledge management, VXDS

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Contemporary Issues in Clinical Pharmacology:

Pediatric Drug Development

Dionna Green, M.D.
Lily Mulugeta, Pharm.D.
Pediatric Clinical Pharmacology Staff
Office of Clinical Pharmacology
OTS, CDER, FDA

Successful Drivers of Pediatric Drug Research

2002
BPCA

- Renewal of pediatric incentive program
- Established process for study of off-patent drugs
- Required public dissesemination of pediatric study results

2003
PREA

- Required pediatric studies of new drug products likely to be used in pediatric patients

2007
FDAAA

- Reauthorized BPCA and PREA
- Pediatric labeling requirement
- Mandated the formation of the Pediatric Review Committee (PeRC)

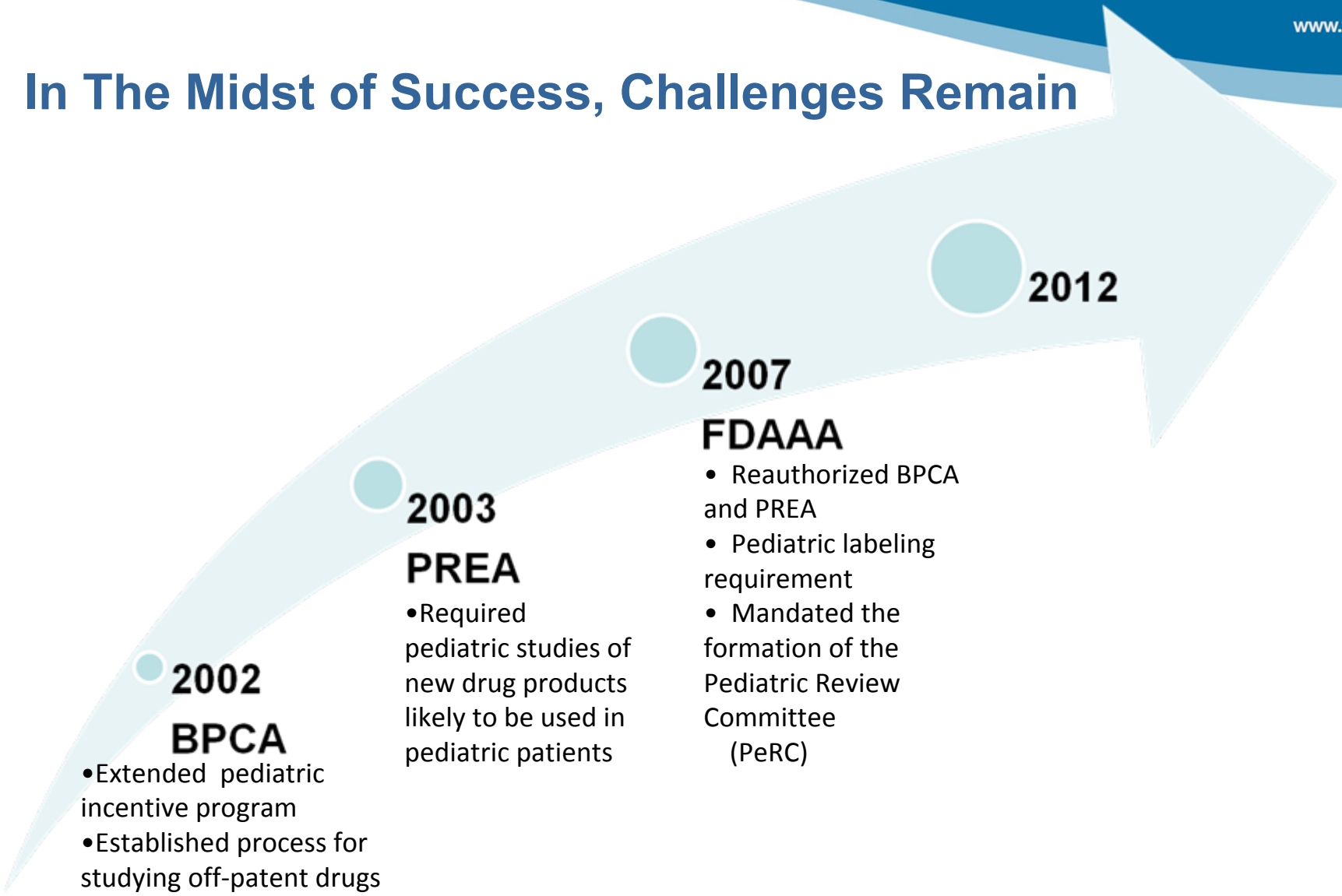
Pediatric Studies Conducted Under BPCA and PREA

Breakdown of FDAAA completed pediatric studies between Sept. 27, 2007 – Dec. 05, 2012

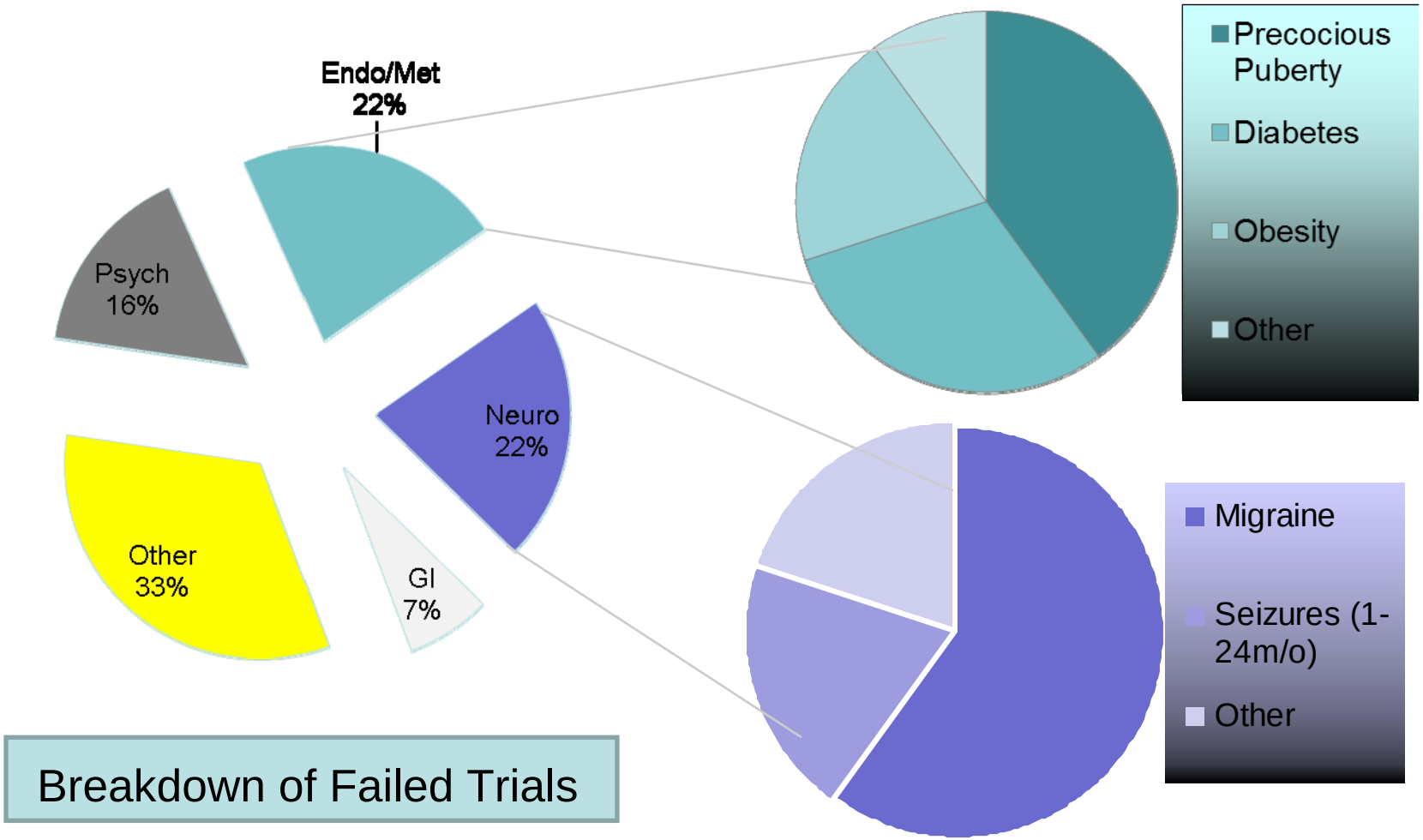
Type of Study	BPCA	BPCA + PREA	PREA	Total
Efficacy/Safety	43	31	199	273
PK/Safety	9	36	21	66
PK/PD	14	8	9	31
Safety	6	4	25	35
Other	3	3	16	22
Total	**75**	**82**	**270**	**425**

Total number of patients in completed FDAAA studies: 175,209
23,339 in BPCA studies; 32,650 in CDER PREA studies;
119,220 in CBER PREA studies (Vaccines and Blood Products)

In The Midst of Success, Challenges Remain



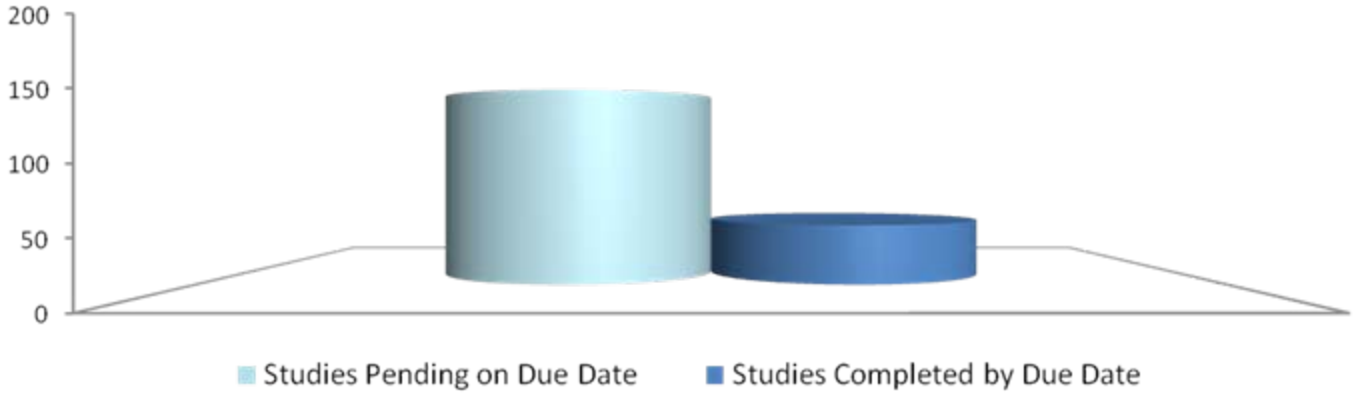
Challenge: Approximately 25% of pediatric trials to fail to result in a labeled indication



Breakdown of Failed Trials

Challenge: Pediatric drug development lags significantly behind adult development

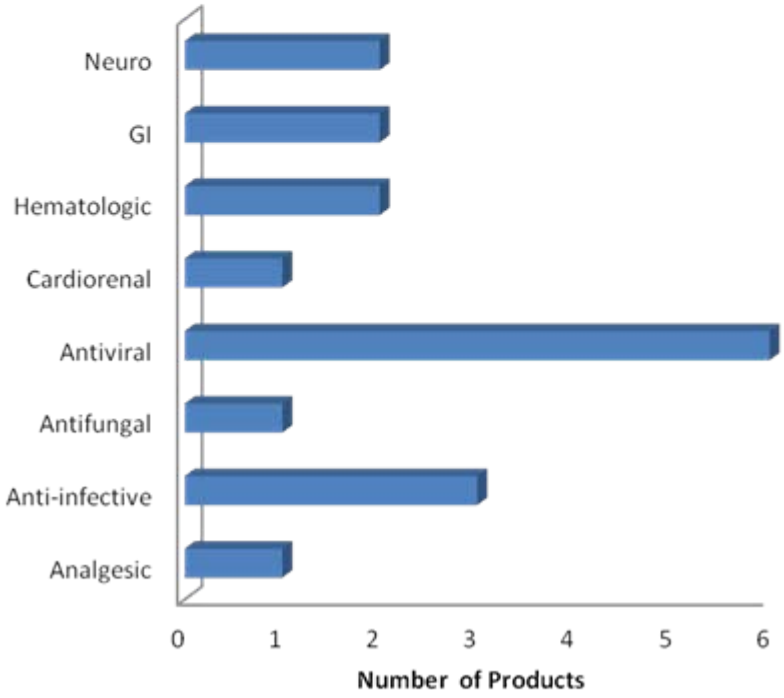
Of the 210 deferred pediatric studies that have reached their due date (since September 2007), the majority are still outstanding



Average time for study completion from issuance of WR by therapeutic area

Data as of Sept. 2012

Challenge: Lack of dosing information in neonates/infants



Medication	% exposed	US FDA labeling for premature infants
Ampicillin	74	None
Gentamicin	68	None
Cefotaxime	36	None
Caffeine citrate	19	None <29 weeks
Furosemide	19	None
Vancomycin	17	None
Beractant	14	Yes
Metoclopramide	11	None
Aminophylline	11	None
Dopamine	10	None

Only 18 out of 161 products studied under FDAAA have PK data in pts. <1yr. of age

Only 1 out of the top 10 products used in the NICU is labeled for use in premature infants

Data as of Dec. 2012

Adapted from Laughon et al. *Expert Rev. Clin. Pharmacol.*, 2011

Building Upon Successful Legislation

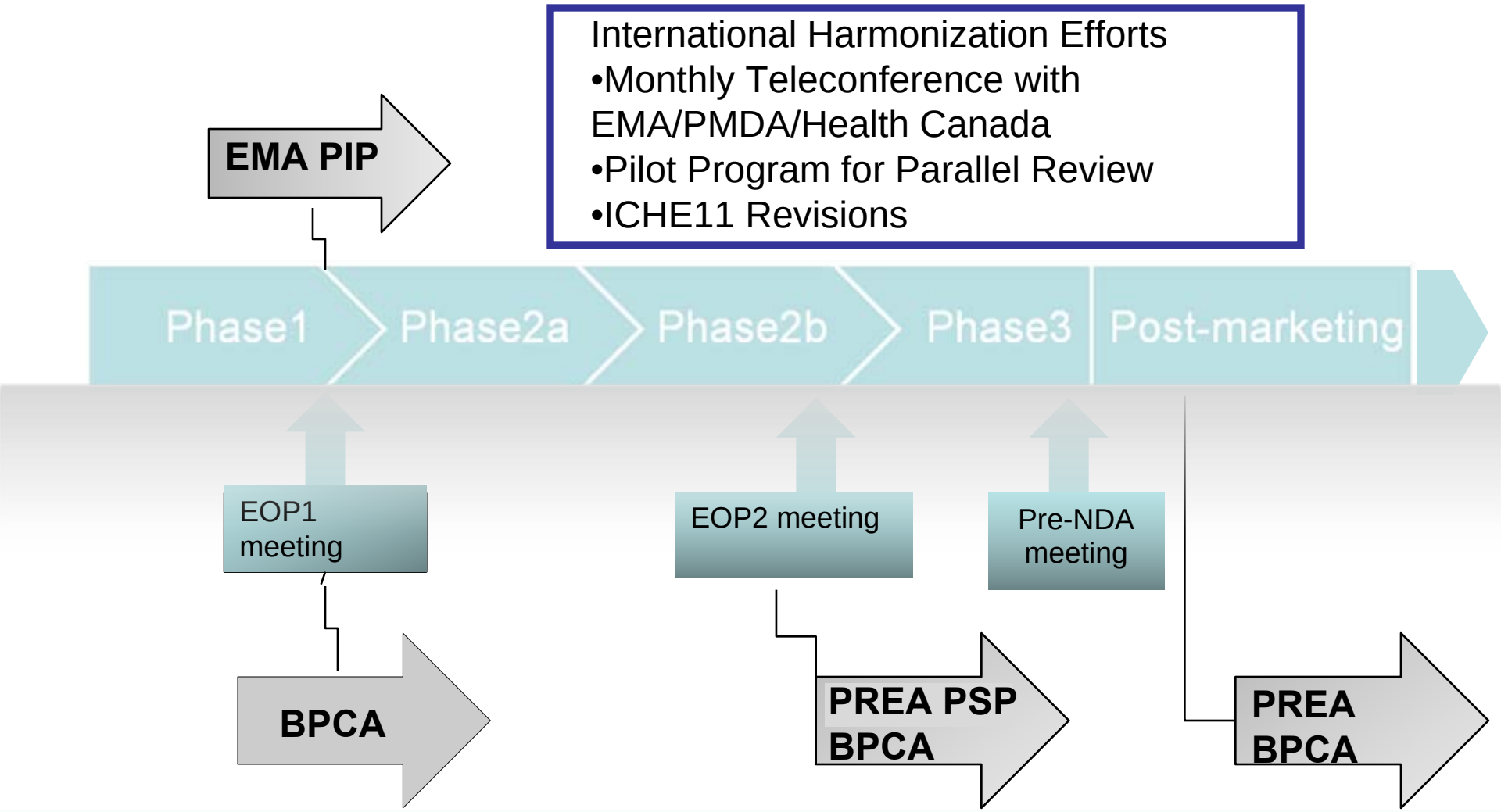
2002
BPCA
- Extended pediatric incentive program
- Established process for studying off-patent drugs
- Required posting of pediatric study results

2003
PREA
- Required pediatric studies of new drug products likely to be used in pediatric patients

2007
FDAAA
- Reauthorized BPCA and PREA
- Pediatric labeling requirement
- Mandated the formation of the Pediatric Review Committee (PeRC)

2012
FDASIA
- Makes permanent BPCA and PREA
- Places emphasis on early study planning
- Establishes timeline for submission and review of PSPs
- Highlights understudied populations

Emphasis on Early Planning of Pediatric Studies



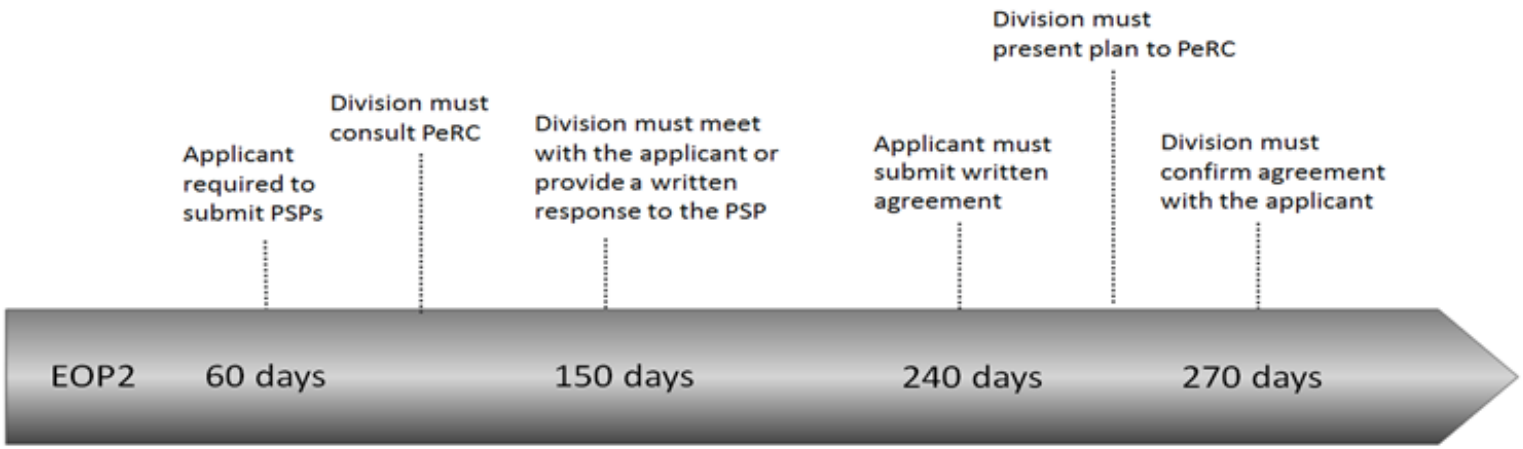
Pediatric Plans

A short paragraph stating that the Applicant plans to conduct pediatric studies (PK, safety, and/or efficacy)

Pediatric Study Plans (PSPs)

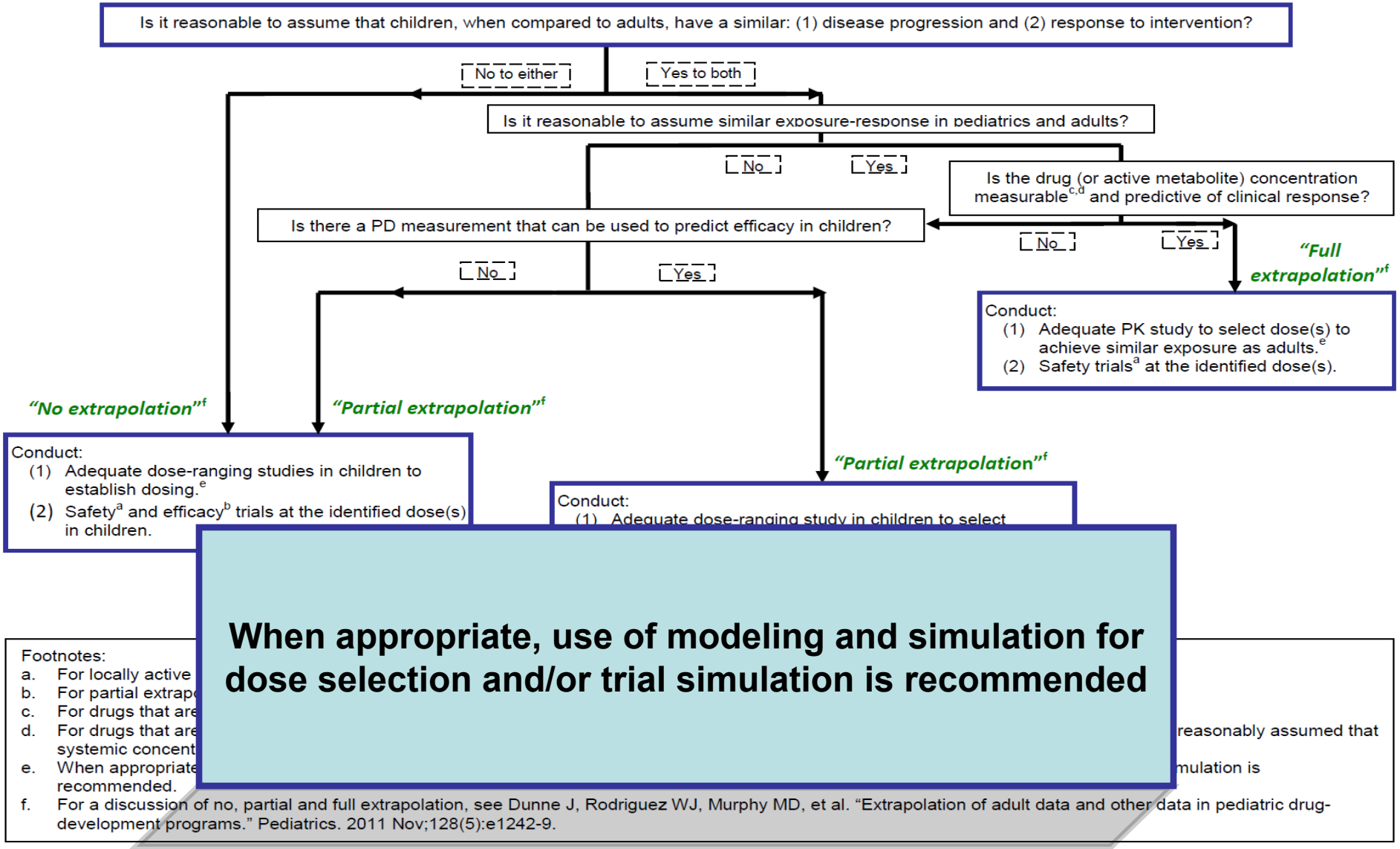
Detailed plan that must include study objectives, study design, age groups, endpoints, statistical approach, and any requests for waivers/deferrals along with supporting information

PSP Review Timeline



All modifications to the PSP must be reviewed by the PeRC

Pediatric Study Planning & Extrapolation Algorithm



When appropriate, use of modeling and simulation for dose selection and/or trial simulation is recommended

Footnotes:
a. For locally active
b. For partial extrapo
c. For drugs that are
d. For drugs that are reasonably assumed that systemic concent
e. When appropriate mulation is recommended.
f. For a discussion of no, partial and full extrapolation, see Dunne J, Rodriguez WJ, Murphy MD, et al. "Extrapolation of adult data and other data in pediatric drug-development programs." Pediatrics. 2011 Nov;128(5):e1242-9.

Pediatric Clinical Pharmacology Staff Charter

IMPROVE PEDIATRIC DRUG DEVELOPMENT

- Reduce unnecessary studies (via i.e., extrapolation, allometric scaling)
- Utilize quantitative tools (i.e., M&S, PBPK) to inform dose selection and trial design
- Employ innovative designs (i.e., E-R, strategic biomarkers, adaptive, enrichment, randomized withdrawal, scavenge sampling, opportunistic)

RESEARCH, POLICY & OUTREACH

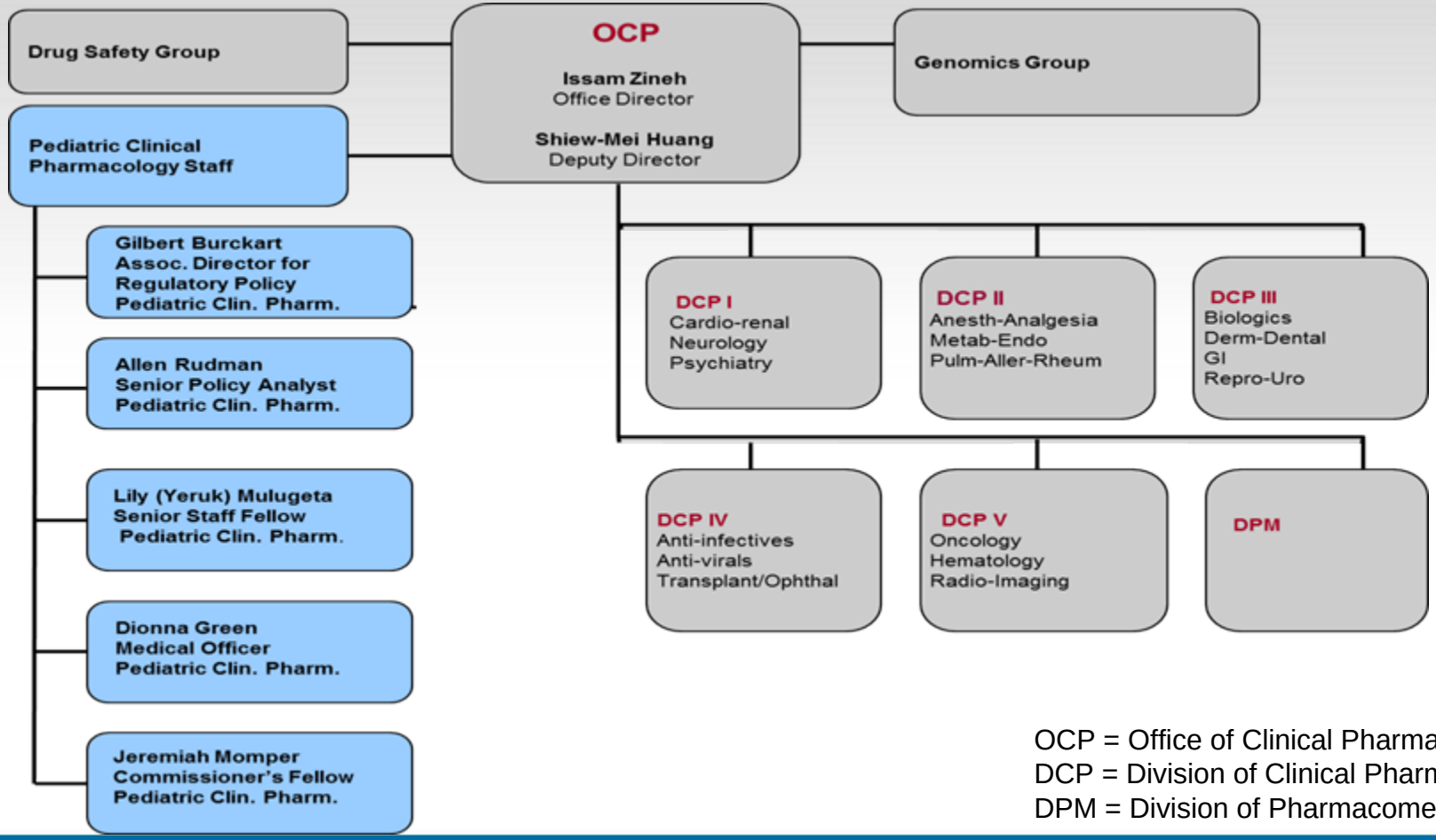
- Conduct and circulate results of high quality scientific and regulatory research
- Develop regulatory policies and procedures to facilitate pediatric drug development
- Train individuals in regulatory science and pediatric clinical pharmacology
- Partner with stakeholders in addressing existing challenges

KNOWLEDGE MANAGEMENT

- Develop comprehensive database of pediatric trials
- Evaluate trial design elements across programs
- Leverage prior data to support future regulatory and scientific decision-making

Pediatric Clinical Pharmacology Staff

Office of Clinical Pharmacology
OTS/CDER/FDA



OCP = Office of Clinical Pharmacology
DCP = Division of Clinical Pharmacology
DPM = Division of Pharmacometrics

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Contemporary Issues in Clinical Pharmacology:

Closing Remarks

Issam Zineh, PharmD, MPH
Director
Office of Clinical Pharmacology
OTS, CDER, FDA